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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
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December 24, 1998

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED
Rolf H. Reinfried, Ph.D.
President
Ganes Chemicals, Inc.
630 Broad Street
Carlstadt, NJ 07072

FILE NO.: 99-NWJ-09

Dear Dr. Reinfried:

This letter concerns FDA inspections of your active pharmaceutical ingredient manufacturing facilities located in Pennsville, NJ, and Carlstadt, NJ, during July 27 - August 19, 1998 and September 8 - 24, 1998, respectively. During both inspections, our investigators documented significant deviations from current Good Manufacturing Practices (cGMPs) in the manufacture of active pharmaceutical ingredients (API's).

These deviations cause the APIs produced at both sites to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (The Act). Section 501(a)(2)(B) of the Act requires that drugs be manufactured, processed, packed, and held in accordance with cGMPs. No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with cGMPs constitutes a failure to comply with the requirements of the Act.

We have reviewed your September 15, 1998 response to the Pennsville inspection and the October 27, 1998 response to the Carlstadt inspection. We conclude that many of the deficiencies noted at both sites have been or are in the process of being corrected. However, your responses to the following observations were determined to be inadequate due to the lack of sufficient detail, explanation, and/or documentation. Unless noted, these deficiencies apply to both the Pennsville and Carlstadt API facilities.

1. **Cleaning procedures for non-dedicated reaction vessels, holding vessels, recrystallizers, centrifuges, and dryers used to produce APIs and intermediates have not been validated.**

We concur with your assessment that progress in validating equipment cleaning procedures has been minimal at best. Our discussions with you on this issue date back to 1993. In January 1996, following the November 15, 17, and December 13, 1995 inspection of the Pennsville facility, you outlined an approach and strategy for implementing a cleaning validation program and provided the Agency with a copy of "Master Plan for Cleaning Validation" of multi-use equipment (approved by Stephen J. Jerger, Manager of Quality Assurance on November 27, 1995). In addition, you submitted a detailed time line for the initial phase of the validation program and committed to executing the first cleaning validation protocol by the end of 1996.

The July 27 - August 19, 1998 inspection, however, disclosed that equipment cleaning validation studies have not been completed for APIs and critical intermediates manufactured at the Pennsville, NJ facility. A similar situation was uncovered during our September 8 - 24, 1998 inspection of the Carlstadt facility. In fact, it appears that cleaning validation studies have not been initiated for most APIs at both sites, since the Master Plan for Cleaning Validation was revised and approved on May 6, 1998.

More than two and a half years have elapsed since you made specific commitments to the Agency to address this deficiency, and you have not yet completed equipment cleaning validation studies. You attribute the delay to an ongoing internal debate regarding cleaning strategy, but it is your responsibility to complete these validation studies. Attachment 28 of your September 15, 1998 response includes a proposed schedule for conducting cleaning validation of 11 API manufacturing trains at the Pennsville site. Attachment 5 of your October 27, 1998 response shows a similar chart for APIs produced at the Carlstadt facility. Both responses state that the schedules are "heavily front-end loaded" with "the majority of the initial cycles completed by the end of the year" at the Pennsville facility, and "a cycle scheduled for completion every month starting with November" at the Carlstadt facility. However, from examining the charts, it is unclear what the task bars and milestones refer to since the charts are not titled and are void of details.

Based on the above, we have little assurance that you will complete cleaning validation studies as proposed in the referenced attachments. Please explain how you plan to complete cleaning validation studies for seven (7) reactor trains in Pennsville before the end of 1998 and seven (7) API trains at the Carlstadt facility by the first quarter of 1999, in conjunction with other corrective actions that are reportedly ongoing or have been promised at both facilities (e.g., completing the installation and qualification of

local enclosures over centrifuges, tray and tumble dryers, dryer charging chutes and membrane presses).

2. **Failure to establish microbiological specifications for deionized water used in the manufacture of active pharmaceutical ingredients. Deionized water is used in the final purification steps for the APIs Methylphenidate HCl, Methadone HCl, Labetalol HCl, Butalbital, and Propoxyphene Napsylate.**

3. **The portable DI units used to produce water for the manufacture of APIs have not been validated from a microbial perspective. The units are tested once a month for microbial contamination, but the firm has no data to demonstrate that this monthly microbiological sample is representative of the whole system.**

Page 8 of your September 15, 1998 response reports that you have now established specifications for deionized water which include limits for total organic carbon conductivity, heterotrophic plate count, total coliforms, and endotoxins. However, according to the testing standard for deionized water (Doc. No. QE0077.3, Issued September 15, 1998), submitted as Attachment 12, testing for these quality attributes will continue to be performed only once per month on random samples taken from the portable DI cylinder units. We consider this test frequency to be inadequate and conclude that monthly microbiological samples are not representative of the system and bear little correlation to the actual microbial quality of the water.

In fact, Page 7 of your September 15, 1998 response emphasizes the inherent difficulties in monitoring a water system consisting of several portable deionizing units. It states:

> "... The need to monitor microbial levels in the DI water was recognized and monitoring began a few years ago with the implementation of testing for Heterotropic plate count, total coliform count, pH and total organic carbon. This monitoring program involved taking monthly samples from each unit on a selected day independent of the status of the individual units. As many as eight units are in use in the plant at this time, and the samples were taken from the units in the plant on the sampling day. This meant that units could have sat idle for a week or more without being used and then been sampled. Other units could have just finished dispensing water to a process."

We reviewed the SOPs for use, sanitation, sampling, and monitoring of the DI water systems included in Attachment 11 of your September 15, 1998 response, and concluded that these revised procedures do not adequately address the difficulties mentioned above and do not support the continued use of the DI water units. For example, sampling of the DI units does not reflect actual use conditions, in that samples are collected after flushing each unit with city water for about 5 $\pm$1 minute, whereas routine use requires discharging a minimum of 60 gallons of city water (two volumes) before metering water into production vessels. Second, sanitation of the in-line filter housings, the connective and discharge hoses of each portable DI unit will be conducted only once per month, which seems too infrequent for DI systems that are inherently prone to microbial contamination. Furthermore, the procedure for monitoring of the DI water system (SOP No. 046.01) only requires an investigation of out-of-spec DI water chemical and microbial results for the sole purpose of determining the impact on APIs produced with water from the deionizer in question. It does not require that the investigation pinpoint the source of the contamination in the DI unit (i.e., contamination of the connective or discharge hoses, contamination of the DI beds, a ruptured .22 micron filter) or remedial action to be taken with the relevant DI unit.

We also have concerns regarding the initial validation phase for the deionized water cylinder units at the Pennsville facility (See Validation Interim Report 98P-VP-5058-01.11, Attachment 11 of the October 27, 1998 response). This study reports that three (3) separate DI cylinder carts were initially staged, secured, and used for purposes of this validation only. The sampling and use of each cart were simulated by three (3) separate plans which reportedly demonstrate that water produced from the DI cylinder units met Ganes testing standard criteria when the units were stored properly in ambient conditions and used daily for a maximum of three (3) days (Plan 1), used every two (2) days for a maximum of six (6) days (Plan 2), used every three (3) days for a maximum of nine (9) days (Plan 3). A fourth plan, which is still ongoing, allows for the testing of each set of cylinders after use in manufacturing for 30 days or more.

Although the interim report shows satisfactory microbial and endotoxin results, we question the validity of this data since the studies simulated constant use of the DI cylinder units, when by the firm's own admission, some units could remain idle for a week or more during routine operations. Second, it appears that the initial studies simulated usage of one DI cylinder cart for a maximum of nine (9) days after sanitization of the unit, but the units are used for up to 30 days before resanitizing during routine production. Plan 4 will attempt to demonstrate the use of DI water units during "normal operation conditions" but Ganes has not defined either normal operating conditions or worst case operating conditions for these DI units.

We believe that you should concentrate your efforts and resources in installing, qualifying and validating centralized purified water systems as referred to in your September 15, 1998 response to the Pennsville inspection.

4. **The HPLC analytical methods used for purity testing of many APIs (e.g., Sodium Phenobarbital, Sodium Amobarbital, and Trazodone) are not adequately validated. There is no data to demonstrate that these methods can accurately recover recurring impurities.**

Your response to the Pennsville inspection acknowledges that additional work on isolating select impurities is needed before you can complete the validation of many HPLC analytical methods. You maintain that work is in progress, but the response fails to provide time frames for completion of this work.

Our review of EIR Exhibit 17 shows that you have completed validation of HPLC methods to detect impurities (Column A) for sixteen APIs and need to complete the validation of the analytical methods for detecting impurities in Phenobarbital/Phenobarbital Sodium and Amobarbital/Amobarbital Sodium. With respect to recovery studies (Column B), you have completed studies for four (4) APIs, three (3) studies are in progress, four (4) have been or are being performed by pharmaceutical manufacturers, and seven (7) recovery studies have yet to be initiated.

Please provide additional documentation detailing your ongoing efforts to validate HPLC analytical methods for detecting impurities in APIs produced at both the Pennsville and Carlstadt facilities. Also provide dates for completion of this work.

5. **Failure to test stability samples at required time intervals. The stability test data for Phenobarbital, Methylphenidate, and Butalbital revealed that in many cases the three (3) month, six (6) month, 12 month, and 24 month scheduled testing was performed late, by as much as three (3) months. There were also cases where the firm performed no testing.**

During our inspection of the Pennsville facility, you attributed the late or missed stability tests of APIs to lack of personnel in the Quality Control laboratory. The September 15, 1998 response reports that you have removed stability testing from the responsibility of the Q.C. release testing laboratory and staffed it as a separate function with three (3) chemists to eliminate the existing backlog. A schedule for eliminating

this stability test backlog was provided as Attachment 18 of your response. You state you are currently in the process of identifying additional resources to expedite this program. Please clarify this statement by providing details and a current assessment whether staff and resources are eliminating this backlog.

The above deficiencies are not to be considered as an all-inclusive list of the deficiencies at your Pennsville and Carlstadt API facilities at the time of our inspections. FDA inspections are not intended to uncover all cGMP deviations that exist at a firm. It is your responsibility to assure adherence with cGMPs. We request that you take prompt action to correct any noted deviations not already corrected and that you conduct a complete evaluation of your API facilities for cGMP compliance.

Please respond within 15 working days with any additional information regarding the steps you are taking to correct the identified deficiencies and assure a comprehensive approach to compliance with cGMPs. Failure to promptly correct these violations may result in regulatory action without further notice. This includes seizure and/or injunction.

Until the FDA reinspects your API facilities and confirms that these deficiencies have been corrected, this office will recommend disapproval of drug applications listing either the Pennsville or Carlstadt facility as suppliers of APIs. Federal agencies are advised of the issuance of Warning Letters to drug or device manufacturers so that they may take this information into account when considering the award of contracts.

Please contact Andrew Ciaccia, Compliance Officer, at the address and telephone numbers shown in the letterhead, if you have any questions or wish to submit additional information detailing corrective actions that you have taken or plan to take to bring your API operations into compliance.

Sincerely,

Douglas I. Ellsworth
Director
New Jersey District